ZOSTAVAX®
[Zoster Vaccine Live (Oka/Merck)]

DESCRIPTION

ZOSTAVAX* is a lyophilized preparation of the Oka/Merck strain of live, attenuated varicella-zoster virus (VZV). The virus was initially obtained from a child with naturally-occurring varicella, then introduced into human embryonic lung cell cultures, adapted to and propagated in embryonic guinea pig cell cultures and finally propagated in human diploid cell cultures (WI-38). Further passage of the virus was performed at Merck Research Laboratories (MRL) in human diploid cell cultures (MRC-5). The cells, virus seeds, virus bulks and bovine serum used in the manufacturing are all tested to provide assurance that the final product is free of adventitious agents. ZOSTAVAX, when reconstituted as directed, is a sterile preparation for subcutaneous administration. Each 0.65-mL dose contains a minimum of 19,400 PFU (plaque-forming units) of Oka/Merck strain of VZV when reconstituted and stored at room temperature for up to 30 minutes. Each dose also contains 31.16 mg of sucrose, 15.58 mg of hydrolyzed porcine gelatin, 3.99 mg of sodium chloride, 0.62 mg of monosodium L-glutamate, 0.57 mg of sodium phosphate dibasic, 0.10 mg of potassium phosphate monobasic, 0.10 mg of potassium chloride; residual components of MRC-5 cells including DNA and protein; and trace quantities of neomycin and bovine calf serum. The product contains no preservatives.

CLINICAL PHARMACOLOGY

Background

Herpes zoster (HZ), commonly known as shingles or zoster, is a manifestation of the reactivation of varicella zoster virus (VZV), which, as a primary infection, produces chickenpox (varicella). Following initial infection, the virus remains latent in the dorsal root or cranial sensory ganglia until it reactivates, producing zoster. Zoster is characterized by a unilateral, painful, vesicular cutaneous eruption with a dermatomal distribution.

Although the rash is the most distinctive feature of zoster, the most frequently debilitating symptom is pain. Pain associated with zoster may occur during the prodrome, the acute eruptive phase, and the postherpetic phase of the infection. This later phase is most commonly referred to as postherpetic neuralgia (PHN).

Serious complications, such as scarring, bacterial superinfection, allodynia, cranial and motor neuron palsies, pneumonia, encephalitis, visual impairment, hearing loss, and death can occur as the result of zoster.

Mechanism of Action

The risk of developing zoster appears to be related to a decline in VZV-specific immunity. ZOSTAVAX was shown to boost VZV-specific immunity, which is thought to be the mechanism by which it protects against zoster and its complications. (See *Immunogenicity*.)

Clinical Studies

Efficacy of ZOSTAVAX was evaluated in the Shingles Prevention Study (SPS),[1] a placebo-controlled, double-blind clinical trial in which 38,546 subjects 60 years of age or older were randomized to receive a single dose of either ZOSTAVAX (n=19,270) or placebo (n=19,276). Subjects were followed for the development of zoster for a median of 3.1 years (range 31 days to 4.90 years). The study excluded people who were immunocompromised or using corticosteroids on a regular basis, anyone with a previous history of HZ, and those with conditions that might interfere with study evaluations, including people with cognitive impairment, severe hearing loss, those who were non-ambulatory and those whose survival was not considered to be at least 5 years. Randomization was stratified by age, 60-69 and

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≥70 years of age. Zoster cases were confirmed by Polymerase Chain Reaction (PCR) [93%], viral culture [1%], or in the absence of viral detection, as determined by the Clinical Evaluation Committee [6%]. Individuals in both vaccination groups who developed zoster were given famciclovir, and, as necessary, pain medications. The primary efficacy analysis included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination (Modified Intent-To-Treat [MITT] analysis).

ZOSTAVAX significantly reduced the risk of developing zoster when compared with placebo (Table 1). Vaccine efficacy for the prevention of HZ was highest for those subjects 60-69 years of age and declined with increasing age.

Table 1
Efficacy of ZOSTAVAX on HZ Incidence Compared with Placebo in the Shingles Prevention Study*

Age group** (yrs.)	ZOSTAVAX			Placebo			Vaccine Efficacy (95% CI)
	# subjects	# HZ cases	Incidence rate of HZ per 1000 person-yrs.	# subjects	# HZ cases	Incidence rate of HZ per 1000 person-yrs.	
Overall	19254	315	5.4	19247	642	11.1	51% (44%, 58%)
60-69	10370	122	3.9	10356	334	10.8	64% (56%, 71%)
70-79	7621	156	6.7	7559	261	11.4	41% (28%, 52%)
≥80	1263	37	9.9	1332	47	12.2	18% (-29%, 48%)

* The analysis was performed on the Modified Intent-To-Treat (MITT) population that included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination.
** Age strata at randomization were 60-69 and ≥70 years of age.

Forty-five subjects were excluded from the MITT analysis (16 in the group of subjects who received ZOSTAVAX and 29 in the group of subjects who received placebo), including 24 subjects with evaluable HZ cases that occurred in the first 30 days postvaccination (6 evaluable HZ cases in the group of subjects who received ZOSTAVAX and 18 evaluable HZ cases in the group of subjects who received placebo).

Suspected HZ cases were followed prospectively for the development of HZ-related complications. Table 2 compares the rates of PHN defined as HZ-associated pain (rated as 3 or greater on a 10-point scale by the study subject and occurring or persisting at least 90 days) following the onset of rash in evaluable cases of HZ.

Table 2
Postherpetic Neuralgia (PHN)* in the Shingles Prevention Study**

Age group (yrs.)†	ZOSTAVAX					Placebo					Vaccine efficacy against PHN in subjects who develop HZ postvaccination (95% CI)
	# subjects	# HZ cases	# PHN cases	Incidence rate of PHN per 1,000 person-yrs.	% HZ cases with PHN	# subjects	# HZ cases	# PHN cases	Incidence rate of PHN per 1,000 person-yrs.	% HZ cases with PHN	
Overall	19254	315	27	0.5	8.6%	19247	642	80	1.4	12.5%	39%†† (7%, 59%)
60-69	10370	122	8	0.3	6.6%	10356	334	23	0.7	6.9%	5% (-107%, 56%)
70-79	7621	156	12	0.5	7.7%	7559	261	45	2.0	17.2%	55% (18%, 76%)
≥80	1263	37	7	1.9	18.9%	1332	47	12	3.1	25.5%	26% (-69%, 68%)

* PHN was defined as HZ-associated pain rated as ≥3 (on a 0-10 scale), persisting or appearing more than 90 days after onset of HZ rash using Zoster Brief Pain Inventory (ZBPI)[2].
** The table is based on the Modified Intent-To-Treat (MITT) population that included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination.
† Age strata at randomization were 60-69 and ≥70 years of age.
†† Age-adjusted estimate based on the age strata (60-69 and ≥70 years of age) at randomization.

The median duration of clinically significant pain (≥3 on a 0-10 point scale) among HZ cases in the group of subjects who received ZOSTAVAX as compared to the group of subjects who received placebo was 20 days vs. 22 days based on the confirmed HZ cases.

Overall, the benefit of ZOSTAVAX in the prevention of PHN can be primarily attributed to the effect of the vaccine on the prevention of herpes zoster. Vaccination with ZOSTAVAX reduced the incidence of PHN in individuals 70 years of age and older who developed zoster postvaccination.

Other prespecified zoster-related complications were reported less frequently in subjects who received ZOSTAVAX compared to subjects who received placebo. Among HZ cases, zoster-related complications were reported at similar rates in both vaccination groups (Table 3).

Table 3
Specific complications* of zoster among HZ cases in the Shingles Prevention Study

Complication	ZOSTAVAX (N = 19,270)		Placebo (N = 19,276)	
	(n = 321)	% Among Zoster Cases	(n = 659)	% Among Zoster Cases
Allodynia	135	42.1	310	47.0
Bacterial Superinfection	3	0.9	7	1.1
Dissemination	5	1.6	11	1.7
Impaired Vision	2	0.6	9	1.4
Ophthalmic Zoster	35	10.9	69	10.5
Peripheral Nerve Palsies (motor)	5	1.6	12	1.8
Ptosis	2	0.6	9	1.4
Scarring	24	7.5	57	8.6
Sensory Loss	7	2.2	12	1.8

N=number of subjects randomized
n=number of zoster cases, including those cases occurring within 30 days postvaccination, with these data available
* Complications reported at a frequency of ≥1% in at least one vaccination group among subjects with zoster.

Visceral complications reported by fewer than 1% of subjects with zoster included 3 cases of pneumonitis and 1 case of hepatitis in the placebo group, and 1 case of meningoencephalitis in the vaccine group.

Immunogenicity

Immune responses to vaccination were evaluated in a subset of subjects enrolled in the Shingles Prevention Study (N=1395). VZV antibody levels (Geometric Mean Titers, GMT), as measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA) 6 weeks postvaccination, were increased 1.7-fold (95% CI: [1.6 to 1.8]) in the group of subjects who received ZOSTAVAX compared to subjects who received placebo; the specific antibody level that correlates with protection from zoster has not been established.

INDICATIONS AND USAGE

ZOSTAVAX is indicated for prevention of herpes zoster (shingles) in individuals 60 years of age and older.

ZOSTAVAX is not indicated for the treatment of zoster or PHN.

CONTRAINDICATIONS

ZOSTAVAX should not be administered to individuals:

- With a history of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine (see WARNINGS).
- With a history of primary or acquired immunodeficiency states including leukemia; lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system; or AIDS or other clinical manifestations of infection with human immunodeficiency viruses (see WARNINGS).
- On immunosuppressive therapy, including high-dose corticosteroids.
- With active untreated tuberculosis.
- Who are or may be pregnant (see PRECAUTIONS, *Pregnancy*).

WARNINGS

Vaccination with a live attenuated vaccine, such as ZOSTAVAX, may result in a more extensive vaccine-associated rash or disseminated disease in individuals who are immunosuppressed. Safety and efficacy of ZOSTAVAX have not been evaluated in individuals on immunosuppressive therapy, nor in individuals receiving daily topical or inhaled corticosteroids or low-dose oral corticosteroids.

Neomycin allergy commonly manifests as a contact dermatitis, which is not a contraindication to receiving this vaccine.[3] Persons with a history of anaphylactic reaction to topically or systemically administered neomycin should not receive ZOSTAVAX (see CONTRAINDICATIONS).

ZOSTAVAX is not a substitute for VARIVAX** [Varicella Virus Vaccine Live (Oka/Merck)] and should not be used in children.

PRECAUTIONS

General

As with any vaccine, adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactic/anaphylactoid reaction occur.

Deferral of vaccination should be considered in acute illness, for example, in the presence of fever >38.5°C (>101.3°F).

The duration of protection after vaccination with ZOSTAVAX is unknown. In the Shingles Prevention Study (SPS), protection from zoster was demonstrated through 4 years of follow-up. The need for revaccination has not been defined.

As with any vaccine, vaccination with ZOSTAVAX may not result in protection of all vaccine recipients.

The use of ZOSTAVAX in individuals with a previous history of zoster has not been studied (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Transmission

In clinical trials with ZOSTAVAX, transmission of the vaccine virus has not been reported. However, post-marketing experience with varicella vaccines suggests that transmission of vaccine virus may occur rarely between vaccinees who develop a varicella-like rash and susceptible contacts. Transmission of vaccine virus from varicella vaccine recipients without a VZV-like rash has been reported but has not been confirmed. The risk of transmitting the attenuated vaccine virus to a susceptible individual should be weighed against the risk of developing natural zoster that could be transmitted to a susceptible individual.

Information for Patients

The health care provider should question the vaccine recipient about reactions to previous vaccines (see CONTRAINDICATIONS). The health care provider should also inform the vaccine recipient of the benefits and risks of ZOSTAVAX. Patients should be provided with a copy of the Patient Information Sheet at the end of this insert, and be given an opportunity to discuss any questions or concerns.

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Vaccinees should also be informed of the theoretical risk of transmitting the vaccine virus to varicella-susceptible individuals, including pregnant women who have not had chickenpox. Patients should also be told that pregnancy should be avoided for three months following vaccination.

Patients should be instructed to report any adverse reactions to their health care provider.

Drug Interactions

Concurrent administration of ZOSTAVAX and antiviral medications known to be effective against VZV has not been evaluated. Concurrent administration of ZOSTAVAX and other vaccines has not been evaluated.

Carcinogenesis, Mutagenesis, Impairment of Fertility

ZOSTAVAX has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with ZOSTAVAX. It is also not known whether ZOSTAVAX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, naturally occurring VZV infection is known to sometimes cause fetal harm. Therefore, ZOSTAVAX should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination (see CONTRAINDICATIONS).

Vaccinees and health care providers are encouraged to report any exposure to ZOSTAVAX during pregnancy by calling (800) 986-8999.

Nursing Mothers

Some viruses are excreted in human milk; however, it is not known whether VZV is secreted in human milk. Therefore, because some viruses are secreted in human milk, caution should be exercised if ZOSTAVAX is administered to a nursing woman.

Pediatric Use

ZOSTAVAX should not be used in children.

Geriatric Use

The median age of subjects enrolled in the largest (N=38,546) clinical study of ZOSTAVAX was 69 years (range 59-99 years). Of the 19,270 subjects who received ZOSTAVAX, 10,378 were 60-69 years of age, 7,629 were 70-79 years of age, and 1,263 were 80 years of age or older.

ADVERSE REACTIONS

In clinical trials, ZOSTAVAX has been evaluated for safety in approximately 21,000 adults. In the largest of these trials, the Shingles Prevention Study (SPS), subjects received a single dose of either ZOSTAVAX (n=19,270) or placebo (n=19,276). The racial distribution across both vaccination groups was similar: White (95%); Black (2.0%); Hispanic (1.0%) and Other (1.0%) in both vaccination groups. The gender distribution was 59% male and 41% female in both vaccination groups. The age distribution of subjects enrolled, 59-99 years, was similar in both vaccination groups.

The Adverse Event Monitoring Substudy (n=3,345 received ZOSTAVAX and n=3,271 received placebo) used vaccination report cards (VRC) to record adverse events occurring from Days 0 to 42 postvaccination (97% of subjects completed VRC in both vaccination groups). In addition, monthly surveillance for hospitalization was conducted through the end of the study, 2 to 5 years postvaccination.

The remainder of subjects in the SPS (n=15,925 received ZOSTAVAX and n=16,005 received placebo) were actively followed for safety outcomes through Day 42 postvaccination and passively followed for safety after Day 42.

Because clinical trials are conducted under conditions that may not be typical of those observed in clinical practice, the adverse reaction rates presented below may not be reflective of those observed in clinical practice.

Serious Adverse Reactions

In the overall study population, serious adverse experiences (SAEs) occurred at a similar rate (1.4%) in subjects vaccinated with ZOSTAVAX or placebo.

In the AE Monitoring Substudy, the rate of SAEs was increased in the group of subjects who received ZOSTAVAX as compared to the group of subjects who received placebo, from Day 0-42 postvaccination (Table 4).

Table 4
Number of Subjects with ≥1 Serious Adverse Experience
(0-42 Days Postvaccination) in the Shingles Prevention Study

Cohort	ZOSTAVAX n/N %	Placebo n/N %	Relative Risk (95% CI)
Overall Study Cohort	255/18671	254/18717	1.01
(all ages)	1.4%	1.4%	(0.85, 1.20)
60-69 years old	113/10100	101/10095	1.12
	1.1%	1.0%	(0.86, 1.46)
70-79 years old	115/7351	132/7333	0.87
	1.6%	1.8%	(0.68, 1.11)
≥80 years old	27/1220	21/1289	1.36
	2.2%	1.6%	(0.78, 2.37)
AE Monitoring Substudy Cohort	64/3326	41/3249	1.53
(all ages)	1.9%	1.3%	(1.04, 2.25)
60-69 years old	22/1726	18/1709	1.21
	1.3%	1.1%	(0.66, 2.23)
70-79 years old	31/1383	19/1367	1.61
	2.2%	1.4%	(0.92, 2.82)
≥80 years old	11/217	4/173	2.19
	5.1%	2.3%	(0.75, 6.45)

N=number of subjects in cohort with safety follow-up
n=number of subjects reporting an SAE 0-42 Days postvaccination

Table 5 displays selected cardiovascular SAEs occurring in the SPS within 42 days postvaccination.

Table 5
Selected Serious Adverse Experiences (SAEs) Reported More Frequently After ZOSTAVAX than After Placebo Days 0-42 Postvaccination in the Shingles Prevention Study

	AE Monitoring Substudy		Entire Study Cohort	
	ZOSTAVAX N = 3326	Placebo N = 3249	ZOSTAVAX N = 18671	Placebo N = 18717
	n (%)	n (%)	n (%)	n (%)
Overall Cardiovascular events by body system	20 (0.6)	12 (0.4)	81 (0.4)	72 (0.4)
Coronary Artery Disease-related conditions*	10 (0.3)	5 (0.2)	45 (0.2)	35 (0.2)

N=number of subjects with safety follow-up
n=number of subjects reporting SAE within the category
* CAD-related conditions: angina pectoris, coronary artery disease, coronary occlusion, cardiovascular disorder, myocardial ischemia, & myocardial infarction

Rates of hospitalizations were similar among subjects who received ZOSTAVAX and subjects who received placebo in the AE Monitoring Substudy, throughout the entire study.

Investigator-determined, vaccine-related serious adverse experiences were reported for 2 subjects vaccinated with ZOSTAVAX (asthma exacerbation and polymyalgia rheumatica) and 3 subjects who received placebo (Goodpasture's syndrome, anaphylactic reaction, and polymyalgia rheumatica).

Deaths

The overall incidence of death occurring Days 0 to 42 postvaccination was similar between vaccination groups during the Days 0-42 postvaccination period; 14 deaths occurred in the group of subjects who received ZOSTAVAX and 16 deaths occurred in the group of subjects who received placebo. The most common reported cause of death was cardiovascular disease (10 in the group of subjects who received ZOSTAVAX, 8 in the group of subjects who received placebo). The overall incidence of death occurring at any time during the study was similar between vaccination groups: 793 deaths (4.1%) occurred in subjects who received ZOSTAVAX and 795 deaths (4.1%) in subjects who received placebo.

Most Common Adverse Reactions

Adverse Events Reported in the AE Monitoring Substudy of the SPS

Injection-site and systemic adverse experiences reported at an incidence ≥1% are shown in Table 6. Most of these adverse experiences were reported as mild in intensity. The overall incidence of vaccine-related injection-site adverse experiences was significantly greater for subjects vaccinated with ZOSTAVAX versus subjects who received placebo (48% for ZOSTAVAX and 17% for placebo).

Table 6
Injection-Site and Systemic Adverse Experiences Reported by Vaccine Report Card in ≥1% of Adults Who Received ZOSTAVAX or Placebo (0-42 Days Postvaccination) in the AE Monitoring Substudy of the Shingles Prevention Study

Adverse Experience	ZOSTAVAX (N = 3345) %	Placebo (N = 3271) %
Injection Site		
Erythema†	33.7	6.4
Pain/tenderness†	33.4	8.3
Swelling†	24.9	4.3
Hematoma	1.4	1.4
Pruritus	6.6	1.0
Warmth	1.5	0.3
Systemic		
Headache	1.4	0.8

† Designates a solicited adverse experience. Injection-site adverse experiences were solicited only from Days 0-4 postvaccination.

The numbers of subjects with elevated temperature (≥38.3ºC [≥101.0ºF]) within 42 days postvaccination were similar in the ZOSTAVAX and the placebo vaccination groups [27 (0.8%) vs. 27 (0.9%), respectively].

The following adverse experiences in the AE Monitoring Substudy of the SPS (Days 0 to 42 postvaccination) were reported at an incidence ≥1% and greater in subjects who received ZOSTAVAX than in subjects who received placebo, respectively: respiratory infection (65 [1.9%] vs. 55 [1.7%]), fever (59 [1.8%] vs. 53 [1.6%]), flu syndrome (57 [1.7%] vs. 52 [1.6%]), diarrhea (51 [1.5%] vs. 41 [1.3%]), rhinitis (46 [1.4%] vs. 36 [1.1%]), skin disorder (35 [1.1%] vs. 31 [1.0%]), respiratory disorder (35 [1.1%] vs. 27 [0.8%]), asthenia (32 [1.0%] vs. 14 [0.4%]).

Adverse Events Occurring after Day 42 postvaccination

AE Monitoring Substudy subjects in the Shingles Prevention Study were monitored for hospitalizations through monthly automated phone queries and the remainder of subjects were passively monitored for safety in this study from Day 43 postvaccination through study end.

Over the course of the study (4.9 years), 51 individuals (1.5%) receiving ZOSTAVAX were reported to have congestive heart failure (CHF) or pulmonary edema compared to 39 individuals (1.2%) receiving placebo in the AE Monitoring Substudy; 58 individuals (0.3%) receiving ZOSTAVAX were reported to have congestive heart failure (CHF) or pulmonary edema compared to 45 (0.2%) individuals receiving placebo in the overall study.

Clinical Safety with High Potency ZOSTAVAX

In an additional clinical study, high potency ZOSTAVAX (203,000 plaque-forming units (pfu)) administered to 461 subjects was compared to a lower potency ZOSTAVAX (57,000 pfu; similar to potencies studied in the Shingles Prevention Study) administered to 234 subjects. Moderate or severe injection-site reactions were more common in the recipients of the higher potency ZOSTAVAX (17%) as compared to the lower potency recipients (9%). Among recipients of the higher potency ZOSTAVAX, 4 subjects (0.9%) reported SAEs (1 case each of angina pectoris, coronary artery disease, depression and enteritis); 1 subject (0.4%) receiving the lower potency ZOSTAVAX reported an SAE (lung cancer).

VZV rashes following vaccination

Within the 42-day postvaccination reporting period in the SPS, noninjection-site zoster-like rashes were reported by 53 subjects (17 for ZOSTAVAX and 36 for placebo). Of 41 specimens that were adequate for PCR testing, wild-type VZV was detected in 25 (5 for ZOSTAVAX, 20 for placebo) of these specimens. The Oka/Merck strain of VZV was not detected from any of these specimens.

Of reported varicella-like rashes (n=59), 10 had specimens that were available and adequate for PCR testing. VZV was not detected in any of these specimens.

In all other clinical trials in support of ZOSTAVAX, the reported rates of noninjection-site zoster-like and varicella-like rashes within 42 days postvaccination were also low in both zoster vaccine recipients and placebo recipients. Of the 17 reported varicella-like rashes and noninjection-site, zoster-like rashes, 10 specimens were available and adequate for PCR testing. The Oka/Merck strain was identified by PCR analysis from the lesion specimens of two subjects who reported varicella-like rashes (onset on Day 8 and 17).

Reporting Adverse Events

The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967 or report online to www.vaers.hhs.gov.[4]

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION.

Do not inject intravascularly.

ZOSTAVAX is administered as a single dose.

Caution: Use only sterile syringes free of preservatives, antiseptics, and detergents for each injection and/or reconstitution of ZOSTAVAX. Preservatives, antiseptics and detergents may inactivate the vaccine virus.

Reconstitute the vaccine using only the diluent supplied. The supplied diluent is free of preservatives or other antiviral substances which might inactivate the vaccine virus.

Use a separate sterile needle and syringe for reconstituting and administration of ZOSTAVAX to prevent transfer of infectious diseases.

ZOSTAVAX is stored frozen and should be reconstituted immediately upon removal from the freezer. The diluent should be stored separately at room temperature or in the refrigerator.

To reconstitute the vaccine: Withdraw the entire contents of the diluent vial into a syringe. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. ZOSTAVAX when reconstituted is a semi-hazy to translucent, off-white to pale yellow liquid.

Inject all of the diluent in the syringe into the vial of lyophilized vaccine and gently agitate to mix thoroughly.

Withdraw the entire contents into a syringe and inject the total volume of reconstituted vaccine subcutaneously; preferably in the upper arm.

THE VACCINE SHOULD BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION, TO MINIMIZE LOSS OF POTENCY.

DISCARD RECONSTITUTED VACCINE IF IT IS NOT USED WITHIN 30 MINUTES.

DO NOT FREEZE reconstituted vaccine.

Needles should be disposed of properly and should not be recapped.

HOW SUPPLIED

No. 4963-00 — ZOSTAVAX is supplied as follows: (1) a package of 1 single-dose vial of lyophilized vaccine, **NDC** 0006-4963-00 (package A); and (2) a separate package of 10 vials of diluent (package B).

No. 4963-41 — ZOSTAVAX is supplied as follows: (1) a package of 10 single-dose vials of lyophilized vaccine, **NDC** 0006-4963-41 (package A); and (2) a separate package of 10 vials of diluent (package B).

Handling and Storage

During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of -20°C (-4°F) or colder.

ZOSTAVAX SHOULD BE STORED FROZEN at an average temperature of -15°C (+5°F) or colder until it is reconstituted for injection. Any freezer, including frost-free, that has a separate sealed freezer door and reliably maintains an average temperature of -15°C or colder is acceptable for storing ZOSTAVAX.

For information regarding stability under conditions other than those recommended, call 1-800-MERCK-90.

Before reconstitution, protect from light.

The diluent should be stored separately at room temperature (20 to 25°C, 68 to 77°F), or in the refrigerator (2 to 8°C, 36 to 46°F).

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